-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

141. The method of claim 138 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

153. The method of claim 152 wherein the air leak is in a pulmonary system.

REMARKS

The claim informalities pointed out by the examiner are first addressed.

Claim informalities

Claims 1, 17, 37, 71, 103, and 138 have been amended to use Markush terminology suggested by the examiner. In the definition of G in each of these claims, "or" has been change to "and."

Claims 2, 9-12, and 15 have been amended as suggested by the examiner to recite an "adhesive composition" instead of "adhesive mixture." The phrase "adhesive composition" has antecedent basis in claim 1.

Claim 16 has been amended to correct a grammatical error. In addition, claim 16 has been amended to depend from claim 1, rather than from claim 15, to place claim 16 in proper dependent form.

Claims 37, 71, 103, and 138 have been amended as suggested by the examiner. Each of these claims has been amended to recite an oligomeric diradical of the formula -R-C(O)-O-$(CH_2)_d$-O-C(O)-. The formula in each of the previous versions of these claims lacked the terminal C(O) group. Support for this amendment can be found in the specification, e.g., at col. 4, line 21.

Each of these claims has also been amended to use proper Markush terminology; in the definition of LM, "or" has been changed to "and." Each of these claims has also been amended to delete inappropriate commas.

Claims 40, 74, 106, and 141 have also been amended. Each of these claims has been amended to recite a lower limit for the concentration of crosslinking agent of 50 mg/ml, instead of 5 mg/ml. Support for this amendment can be found, e.g., in the original claim 5. These claims, as amended, properly limit the scope of the claims from which they depend.

Claims 51 and 153 have been amended to recite "a pulmonary system" instead of "the pulmonary system" to provide antecedent basis.

Claims 130-132 have been amended to correct the dependencies of these claims.

The basis of the rejection of claim 157 is that "[c]laim 157 appears to recite the same limitation found in claim 119." (office action at page 7, carryover paragraph) Applicants submit that claim 157 is different in scope than claim 119. Claim 119 recites curing a composition on tissue "to bond said composition to the tissue and to provide a substantive cured matrix." (emphasis added) The cited language refers to the adhesion of the composition to tissue. Claim 157, on the other hand, recites "curing the composition to form a matrix to bind tissue." (emphasis added) As a non-limiting example of what is meant by a matrix binding tissue, a matrix may bind two different flaps of tissue on either side of a cut to hold the two flaps in close proximity.

In view of the discussion above, the rejection of the claims as indefinite may be withdrawn.

No new matter has been added by these amendments.

The remarks below address the other objections and rejections in the order they appear in the office action.

Petition to correct inventorship

The petition has been granted. As requested, a copy of the certificate of correction is attached, as Exhibit A.

Disclosure informalities

As requested, a clean copy of the specification page including column 3 is attached hereto, as Exhibit B.

Reissue oath

The objection to the oath reasons that it fails to provide specific identification of at least one error in the patent. Applicants submit that the oath filed with the reissue application is adequate. Nevertheless, applicants have filed herewith a supplemental oath, a copy of which is provided as Exhibit C. The supplemental oath in part recites:

> Claim 12 recites a method of sealing tissue that involves curing adhesive mixtures that include "serum albumin," while the specification more broadly describes methods of treatment relating to albumin proteins not limited to serum albumin protein.

Applicants request that the objection to the oath be withdrawn.

New matter/written description

All of these rejections relate to amendments to the claims. Each rejection is discussed in turn below.

Serum albumin

New reissue claims 18, 22, 84, and 114 were rejected for reciting "albumin protein". The basis of this rejection is that the disclosure of albumin proteins in the specification is limited to serum albumin. Applicants traverse.

The specification expressly states that the invention is not limited to serum proteins (col. 3, lines 19-29):

> Serum lipoproteins are particularly well suited... Other soluble proteins in addition to serum lipoproteins, are also suitable for use in the present invention.

Examples using non-serum albumin, chicken egg albumin, are disclosed at, e.g., col. 8, lines 57-58 and in Tables 1 and 4.

The specification, therefore, does indeed describe the use of albumin protein, not limited to serum albumin.

As a result, applicants request that this rejection be withdrawn.

Peel strength

New reissue claims 27, 61, 93, and 128 were rejected for reciting a peel strength of "about 0.08 lb/in or more", without specifying an upper limit. The basis of this rejection is that the original disclosure is limited to peel strengths no higher than about 0.6 lb/in because that is the highest peel strength illustrated in Fig. 2. Applicants traverse.

There is no issue that the disclosure in applicants' specification enables and provides a written description that supports claims without any specific reference to peel strength. Rather, the rejection focuses only on dependent claims that recite specific lower limits for the peel strength. Moreover, there is no issue that the lower limits for the peel strengths are properly supported. These are expressly set forth in Fig. 2. The rejection, therefore, can only be based on reasoning that Fig. 2 somehow excludes peel strengths greater than the maximum value it discloses. But this is improper. Cf. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1566 (Fed. Cir. 1991) ("The court further erred in applying a legal standard that essentially required the drawings of the '081 design application to necessarily exclude all diameters other than those within the claimed range. We question whether any drawing could ever do so.")

Fig. 2 does not exclude peel strengths beyond 0.6 lb/in. In fact, just the opposite is true. The data in Fig. 2 is assembled to demonstrate how to vary peel strength as a function of crosslink agent concentration. Guidance on how to vary peel strength would not be construed by a person of ordinary skill in the art as limiting the maximum.

Moreover, the specification makes clear that peel strength is a measure of adhesive strength (col. 13, line 54), and the practical requirements would be understood (col. 1, line 47 et seq.). Cf. Ralston Purina Co. v. Far-Mar Co, Inc. 772 F.2d 1570, 1576 (Fed. Cir. 1985)("[O]pen ended claims... would be limited by what a person skilled in the art would understand to be workable.") Of course, it is not the law that applicants' specification must expressly state each claim limitation. Rather, to satisfy the written description requirement, the specification must reasonably convey that applicant was in possession of the claimed invention. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1566 (Fed. Cir. 1991)("[R]anges found in [an] applicant's claims need not correspond exactly to those disclosed in [a] parent application; [the] issue is whether one skilled in the art could derive the claimed ranges from [the] parent's disclosure" quoting Ralston Purina, 772 F.2d at 1575.)

As a result, the specification conveys to a person of ordinary skill in the art the peel strengths as claimed. Applicants request that these rejections be withdrawn.

Burst Strength

Claims 1, 17, 28-31, 62-65, 94-97 and 129-132 were rejected based on their recitations of specific burst strengths. These rejections follow three lines of reasoning.

First, similar to the rejections addressed above regarding peel strength, these rejections reason that because the highest burst strength described in the specification is 196 mmHg, claims reciting a specific lower limit must also recite this specific upper limit.

But the data in Example 9 and Tables 3 and 4 provide guidance on how to vary burst strength. For example, burst strengths of compositions with various protein types, pH, membrane types, and cure times are demonstrated. Burst strengths beyond 196 mmHg are clearly not excluded and the specification would convey to a person of ordinary skill in the art the burst strengths as claimed.

As a result, applicants request that the rejections relying on this basis be withdrawn.

Second, the rejections reason that claims reciting burst strengths below 30 mmHg are impermissible because the disclosure does not describe a burst strength below 30 mmHg when serum albumin is used. But, as applicants pointed out above, neither the claims nor the specification are limited to serum albumin. The claims recite "albumin protein". Besides serum albumin, the specification describes non-serum albumin proteins, such as chicken egg albumin.

In Table 4, the burst strength for a composition including chicken egg albumin is about 14 mmHg with a standard deviation of 3 mmHg, giving a minimum burst strength of about 11 mmHg. The specification, therefore, does indeed describe burst strengths below about 30 mmHg when non-serum albumin proteins are used.

As a result, applicants request that the rejections relying on this basis be withdrawn.

Finally, the rejections reason that claims reciting "a burst strength greater than about 10 mmHg" are not supported by a written description in the specification.

But the specification conveys that applicants were in possession of compositions having a burst strength greater than about 10 mmHg. In Table 4, the burst strengths for various examples of applicants' compositions are compared to a "control sealant material"(col. 15, line 31), which is a conventional fibrin glue.

The data illustrates that the maximum burst strength for the control is about 10 mmHg (nominal about 8 mmHg, standard deviation 2 mmHg), while the burst strengths for examples of applicants' compositions are greater than about 10 mmHg. In particular, the burst strength for a composition including chicken egg albumin is about 11 mmHg (Table 4, column 17) and burst strengths for compositions including other albumin proteins are well above 10 mmHg.

As a result, the specification conveys to a person of ordinary skill in the art that applicants were in possession of the claimed invention involving applying and curing a mixture including an albumin protein to form a substantive matrix that has a burst strength greater than the control, i.e., greater than about 10 mmHg.

Applicants request that the rejections relying on this basis be withdrawn.

Terminal C(O)-group

Claims 37, 71, 103, and 138 were rejected for introducing new matter because they are missing a terminal C(O)-group in a chemical formula. These claims have been amended to include this group, consistent with the original patent claims.

Crosslinking Agent Concentration

Claims 40, 74, 106, and 141 were rejected for introducing new matter because they recite a crosslinking agent concentration as low as 5 mg/ml. These claims have been amended to recite a limit of about 50 mg/ml, consistent with the original patent claims.

Recapture Rule

The new reissue claims, claims 18-162, were rejected for violating the recapture rule. This rejection is traversed.

An approach to application of the recapture rule involves a determination of whether and in what aspects the reissue claims are broader than the patent claims, whether these aspects relate to surrendered subject matter, and whether the reissue claims are narrower in scope than the amended or cancelled claims. In re Clement, 131 F.3d 1464, 1468-70 (Fed. Cir. 1997).

The new reissue claims are method of treatment claims. For example, claim 18 is a method of treating tissue to prevent or control air or fluid leaks:

> A method of treating tissue to prevent or control air or fluid leaks comprising:

providing a composition to tissue, said composition including an albumin protein and a crosslinking agent, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix.

The Barrows et al. patent has method of treatment claims. These are claims 9-12, all of which are independent claims. Claim 12, for example, is a method of preventing or controlling blood or other fluid leaks:

> An *in vivo* method to seal tissue comprising the step of topically applying and bonding the adhesive mixture of claim 1 to tissue to prevent or control blood or other fluid leaks.

As evident, this method of treatment claim imports claim 1, a composition claim, to describe the mixture in the applying step. The new independent reissue claim is broader than the patent claim, at least in the aspects pointed out in the office action. Basically, the office action points out that the reissue claim:

- recites providing a composition including "albumin protein" not "serum albumin protein";
- does not recite providing a specific protein concentration, crosslinking agent concentration, or burst pressure.

On the other hand, comparing reissue claim 18 to the method of treatment claim that was amended (see particularly claim 21 and claim 1, as filed), it is clear that the reissue method of treatment claim is narrower in certain aspects. In particular, the reissue claim:

- recites providing a composition including "albumin protein" where the amended method of treatment claim recites "protein";

- recites, in combination, "curing said composition on tissue to bond said composition to tissue and to provide a substantive cured matrix", where the amended method of treatment claims did not recite this limitation.

Reissue claims that are broader in some aspects but narrower than the cancelled or amended claims in others may be allowable if the narrower aspects are relevant to the prior art rejections in the original prosecution. In re Clement 131 F.3d 1464, 1470 (Fed. Cir. 1997); Manual of Patent Examining Procedure, Sec. 1412.02 ("Where such claims also include some narrowing limitation not present in the claims deliberately cancelled in the application...If the narrowing limitation has a material aspect to it, then there is no recapture.").

As discussed above, the reissue claims are narrower than any of the original method of treatment claims that were rejected in the prosecution because they recite the combination of providing albumin protein and polyoxyethylene crosslinking agent on tissue and curing the composition on the tissue to bond the composition to the tissue and provide a substantive cured matrix.

These features are clearly germane to the arguments applicants made during prosecution of the original patent. In the response filed June 7, 1995, applicant argued:

> Importantly, there is nothing in the references, alone or combined, which suggests that the recited combination of serum albumin protein and crosslinking agent would function as an *in vivo* tissue adhesive or sealant nor is there any motivation to combine the references in the manner suggested.

And in the response filed January 26, 1996:

> Importantly, there is nothing in the references, alone or combined, which suggests that the recited combination of serum albumin protein and crosslinking agent would function as *in vivo* tissue adhesive or sealant nor is there any motivation to combine the references in the manner suggested.

As a result, there can be no question that the reissue claims are narrower than the method of treatment claims that were amended in the prosecution in ways that are material.

Moreover, in view of the prosecution history as a whole, applicants did not surrender the subject matter of the method of treatment reissue claims. "To determine whether an applicant surrendered particular subject matter, we look to the prosecution history for arguments and changes to the claims made in an effort to overcome a prior art rejection." In re Clement 131 F.3d 1464, 1469 (Fed. Cir. 1997). For example, applicants did not specifically argue the distinction between "serum" albumin and albumin protein. Cf. In re Richman 409 F.2d 269, 274-275 (CCPA 1969) ("We therefore find... [no authority] for the proposition that a limitation added to a claim in obtaining its allowance cannot be broadened, under present statutory law, by reissue if the limitation turns out to be more restrictive than the prior art required.").

Finally, in considering the "error" requirement, we keep in mind that the reissue statute is "based on fundamental principles of equity and fairness, and should be construed liberally." In re Weiller, 790 F.2d 1576, 1579 (Fed. Cir. 1986). One of the most commonly asserted "errors" in support of a broadening reissue is the failure to appreciate the full scope of the invention during the prosecution of the original patent application. In re Wilder, 736 F.2d 1516, 1519 (Fed. Cir. 1984). Here, the reissue claims clearly cover aspects of applicants' discoveries relating to methods of treatment that were innocently not fully appreciated during the original prosecution.

The other independent reissue claims (claims 52, 84, 119) are also methods of treatment that require providing albumin protein and should not be subject to the recapture rule at least for the reasons discussed above. In addition, the dependent reissue claims, of course, include further features. As a result, these claims avoid recapture issues for still additional reasons but should be allowable at least for the reasons discussed above with respect to the independent claims.

Applicants request that the recapture rule rejections be withdrawn.

Prior Art

Claims 119, 120, 128-134 and 157 were rejected in view of Doi. Applicants traverse.

Claim 119 is the only independent claim in the rejected group. It recites a method of treating tissue. The method includes: (1) providing a composition to tissue, the composition including an albumin protein and a crosslinking agent, the crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with the protein; and (2) curing the composition on the tissue to bond the composition to the tissue and to provide a substantive cured matrix.

Doi et al., on the other hand, merely describes a gel product that is formed remotely from the patient and has stickiness so that it can be self-adhered to the patient's skin. A feature of the product is that it can be removed from skin and then re-adhered. The product is provided as an ointment or a pack agent or sheet pack or sheet structure for treating inflammation or cosmetic use:

> This invention relates to hydrated adhesive gels, especially hydrated adhesive gels for a self-adhesion cataplasm and pack agents having sheet shape. (Doi et al. col. 1, line 5-15).

The Examples in Doi et al. describe the process of manufacture, which includes mixing the reactants, applying the solution to a piece of fabric, and covering with a polyethylene film. The product can be tested by cutting it into squares which are applied to skin.

As a result, Doi et al. does not teach providing a composition to tissue and curing the composition on the tissue to bond and to provide a substantive cured matrix. Nor would Doi et al. suggest to a person of ordinary skill in art a method that includes providing the composition to tissue and curing on tissue

to bond to tissue and to provide a substantive cured matrix for an effective treatment.

Allowance is requested.

Kindly apply any amount due or credit to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Sept. 30, 1999

Christine P. Ballon
Reg. No. 41,611

John J. Gagel
Reg. No. 33,499

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804

Telephone: 617/542-5070
Facsimile: 617/542-8906
395253.B11

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UNITED STATES PATENT AND TRADEMARK OFFICE

Certificate

Patent No. 5,583,114 Patented: December 10, 1996

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without any deceptive intent, improperly sets forth the inventorship.

Accordingly, it is hereby certified that the correct inventorship of this patent is: Matthew T. Scholtz, Woodbury; Thomas H. Barrows, Cottage Grove; Terry W. Lewis, Woodbury; and Myhanh T. Truong, Blaine, all of Minn.

Signed and Sealed this Thirteenth Day of April, 1999.

Cecilia Tsang

CECILIA J. TSANG
Supervisory Patent Examiner
Art Unit 1654

FIG. 3 is a schematic diagram of an apparatus used to measure burst strength of an adhesive sealant composition.

DETAILED DESCRIPTION

The present invention is related to an adhesive composition which has high mechanical strength, flexibility, fast cure rate and sufficient adhesion needed to bond and/or seal tissue in vivo. The adhesive composition is made of two components, a buffered basic protein solution and a bifunctional crosslinking agent. The buffered protein solution and the bifunctional crosslinking agent are typically prepared using commercially available materials and established synthetic methods. The use of known, commercially available materials in the preparation of the adhesive composition provides a benefit in the practice of this invention because most of these materials generally have a history of clinical safety and/or use.

Suitable proteins for use in the present adhesive composition include nonimmunogenic, water soluble proteins. Serum lipoproteins are particularly well suited for this purpose because these proteins bind to lipids and also exhibit a relatively high elasticity in the natured or semi-natured state. These properties are believed to provide a cured matrix which is strong as well as pliant and elastic. Other soluble proteins, in addition to serum lipoproteins, are also suitable for use in the present invention. Aqueous mixtures of proteins such as derivatives of elastin, fibrinogen and collagen may be used in the present invention.

Preferred buffered protein solutions which may be used in the present adhesive composition include concentrated aqueous serum albumin protein mixtures that are buffered to a pH of between about 8.0–11.0 where the buffer concentration is in a range of about 0.01–0.25 molar. Suitable buffer systems include buffers which are physiologically and/or clinically acceptable such as known carbonate or phosphate buffer systems, provided the buffer does not adversely react with or otherwise alter the crosslinking agent. A preferred buffer system is a carbonate/bicarbonate buffer system at a pH value of about 9.0–10.5 at a concentration in the range of 0.05–0.15 molar.

Serum albumin protein is readily isolated from serum using known isolation processes. In addition, it is possible to produce human serum albumin from genetically transformed cells. See, for example, the reports of Quirk et al., *Biotechnology and Applied Biochemistry*, 11:273–287 (1989), Kalman et al., *Nucleic Acids Research*, 18:6075–6081 (1990), Sleep et al., *Biotechnology*, 8:42–46 (1990), and Sijmons et al., *Biotechnology*, 8:217–221 (1990). The ability to produce human serum albumin recombinantly provides the benefit that protein produced by this method will be free of pathogens, viruses or other contaminants that might contaminate albumin that is isolated directly from serum.

When used in the present buffered mixtures it has been found that the serum albumin is not denatured. Because the albumin is not denatured before it is used it is believed that the albumin proteins retain their natured, coiled conformation and thus, after being crosslinked during the curing process to provide a gel-like solid, the cured adhesive retains sufficient flexibility to provide a suitable adhesive matrix.

A variety of suitable crosslinking agents may be used in the present invention. Preferred crosslinking agents include a polyethylene glycol or polyoxyethylene chain portion (—PEG—), an activated leaving group portion (—G) and a linking moiety (—LM—) which binds the —PEG— portion